2'-O-(trans 2-methoxyphenyl) -- 2'-O-(2MP)

[0075] Structural details for duplexes incorporating such 2-O-substituents were analyzed using the described AMBER force field program on the Indigo2 SGI machine. The simulated structure maintained a stable A-form geometry throughout the duration of the simulation. The presence of the 2' substitutions locked the sugars in the C3'-endo conformation.

[0076] The simulation for the TMCHL modification revealed that the 2'-O-(TMCHL) side chains have a direct interaction with water molecules solvating the duplex. The oxygen atoms in the 2'-O-(TMCHL) side chain are capable of forming a water-mediated interaction with the 3' oxygen of the phosphate backbone. The presence of the two oxygen atoms in the 2'-O-(TMCHL) side chain gives rise to favorable gauche interactions. The barrier for rotation around the O-C-C-O torsion is made even larger by this novel modification. The preferential preorganization in an A-type geometry increases the binding affinity of the 2'-O-(TMCHL) to the target RNA. The locked side chain conformation in the 2'-O-(TMCHL) group created a more favorable pocket for binding water molecules. The presence of these water molecules played a key role in holding the side chains in the preferable gauche conformation. While not wishing to be bound by theory, the bulk of the substituent, the diequatorial orientation of the substituents in the cyclohexane ring, the water of hydration and the potential for trapping of metal ions in the conformation generated will additionally contribute to improved binding affinity and nuclease resistance of oligonucleotides incorporating nucleosides having this 2'-O-modification.

[0077] As described for the TMCHL modification above, identical computer simulations of the 2'-O-(TMCPL), the 2'-O-(2MP) and 2'-O-(TUCHL) modified oligonucleotides in aqueous

solution also illustrate that stable A-form geometry will be maintained throughout the duration of the simulation. The presence of the 2' substitution will lock the sugars in the C3'-endo conformation and the side chains will have direct interaction with water molecules solvating the duplex. The oxygen atoms in the respective side chains are capable of forming a water-mediated interaction with the 3' oxygen of the phosphate backbone. The presence of the two oxygen atoms in the respective side chains give rise to the favorable gauche interactions. The barrier for rotation around the respective O-C-C-O torsions will be made even larger by respective modification. The preferential preorganization in A-type geometry will increase the binding affinity of the respective 2'-O-modified oligonucleotides to the target RNA. The locked side chain conformation in the respective modifications will create a more favorable pocket for binding water molecules. The presence of these water molecules plays a key role in holding the side chains in the preferable gauche conformation. The bulk of the substituent, the diequatorial orientation of the substituents in their respective rings, the water of hydration and the potential trapping of metal ions in the conformation generated will all contribute to improved binding affinity and nuclease resistance of oligonucleotides incorporating nucleosides having these respective 2'-O-modification.

[0078] Preferred for use as the B-form nucleotides for eliciting RNase H are ribonucleotides having 2'-deoxy-2'-S-methyl, 2'-deoxy-2'-methyl, 2'-deoxy-2'-amino, 2'-deoxy-2'-mono or dialkyl substituted amino, 2'-deoxy-2'-fluoromethyl, 2'-deoxy-2'-difluoromethyl, 2'-deoxy-2'-trifluoromethyl, 2'-deoxy-2'-methylene, 2'-deoxy-2'-fluoromethylene, 2'-deoxy-2'-difluoromethylene, 2'-deoxy-2'-ethyl, 2'-deoxy-2'-ethylene and 2'-deoxy-2'-acetylene. These nucleotides can alternately be described as 2'-SCH_3 ribonucleotide, 2'-CH_3 ribonucleotide, 2'-NH_2 ribonucleotide 2'-NH(C_1-C_2

alkyl) ribonucleotide, 2'-N(C_1-C_2 alkyl)$_2$ ribonucleotide, 2'-CH_2F ribonucleotide, 2'-CHF_2 ribonucleotide, 2'-CF_3 ribonucleotide, 2'=CH_2 ribonucleotide, 2'=CHF ribonucleotide, 2'=CF_2 ribonucleotide, 2'-C_2H_5 ribonucleotide, 2'-CH=CH_2 ribonucleotide, 2'-C≡CH ribonucleotide. A further useful ribonucleotide is one having a ring located on the ribose ring in a cage-like structure including 3',O,4'-C-methyleneribonucleotides. Such cage-like structures will physically fix the ribose ring in the desired conformation.

[0079] Additionally, preferred for use as the B-form nucleotides for eliciting RNase H are arabino nucleotides having 2'-deoxy-2'-cyano, 2'-deoxy-2'-fluoro, 2'-deoxy-2'-chloro, 2'-deoxy-2'-bromo, 2'-deoxy-2'-azido, 2'-methoxy and the unmodified arabino nucleotide (that includes a 2'-OH projecting upwards towards the base of the nucleotide). These arabino nucleotides can alternately be described as 2'-CN arabino nucleotide, 2'-F arabino nucleotide, 2'-Cl arabino nucleotide, 2'-Br arabino nucleotide, 2'-N_3 arabino nucleotide, 2'-O-CH_3 arabino nucleotide and arabino nucleotide.

[0080] Such nucleotides are linked together via phosphorothioate, phosphorodithioate, boranophosphate or phosphodiester linkages. particularly preferred is the phosphorothioate linkage.

[0081] Illustrative of the B-form nucleotides for use in the invention is a 2'-S-methyl (2'-SMe) nucleotide that resides in C2' endo conformation. It can be compared to 2'-O-methyl (2'-OMe)nucleotides that resides in a C3' endo conformation. Particularly suitable for use in comparing these two nucleotides are molecular dynamic investigations using a SGI [Silicon Graphics, Mountain View, CA] computer and the AMBER [UCSF, San Francisco, CA] modeling software package for computer simulations.

[0082] Ribose conformations in C2'-modified nucleosides containing S-methyl groups were